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The endothelin-type-A receptor in dilated cardiomyopathy: another key player?

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Chronic impairment of left ventricular function activates various homeostatic mechanisms. Most of them are vasoconstrictor, positive chronotropic and inotropic stimuli which aim at maintaining adequate cardiac output and organ perfusion. Ultimately, however, they have adverse effects on the cardiovascular system and contribute significantly to the process of cardiovascular remodelling and, thereby, morbidity and mortality. Importantly, strategies to remove the adverse influence of an activated renin-angiotensin-aldosterone and sympathetic nervous system by treatment with angiotensin converting enzyme inhibitors^[1], the aldosterone antagonist spironolactone^[2], and beta-blockers^[3] have proven extremely successful.

In recent years, the endothelium has been recognised as a source of potent vasoactive substances, among them the vasoconstrictor peptide endothelin-1 (ET-1)^[4]. ET-1 is one of the most potent and long lasting vasoconstrictors known. In addition, ET-1 is an important growth promoter^[5].

The effects of ET-1 are mediated by two distinct receptors: the ET-1 selective ET_A and the non-isopeptide-selective ET_B receptor. The vasoconstrictor effects of ET-1 are predominantly mediated by ET_A receptors; however, vascular smooth muscle cells also express ET_B receptors which contribute to ET-1 mediated vasoconstriction. ET_B receptors also exist

on endothelial cells and modulate the vasoconstrictor effects of ET-1 through generation of nitric oxide and/or prostacyclin. Moreover, adrenal ET-1 receptors mediate release of aldosterone and ET_B receptors on renal tubuli mediate diuresis and natriuresis in dogs. While the majority of functional ET-1 receptors in cardiac myocytes, particularly in failing myocardium, are of the ET_A type and myocyte growth, accordingly, is an ET-A receptor mediated process, fibroblasts contain both ET_A and ET_B receptors. Thus, collagen synthesis seems to be mediated through both ET_A and ET_B receptors. In addition, the ET_B receptors serve as clearance receptors for ET-1 from the circulation (for review^[6]).

Several lines of evidence suggest that the endothelin system plays an important role in human heart failure (for review^[7]). Thus, plasma ET-1 levels are increased in more severely symptomatic patients with heart failure and the extent of haemodynamic impairment is closely related to plasma ET-1 levels. The main source of elevated ET-1 in heart failure appears to be the pulmonary circulation and elevated levels correlate well with pulmonary vascular tone and pulmonary hypertension. Elevated angiotensin II and norepinephrine levels in heart failure also increase ET-1 production and release. While endogenous ET-1 has a positive inotropic effect in normal myocardium it has a negative inotropic effect in the failing myocardium of patients with dilated cardiomyopathy. ET-1 plasma levels correlate inversely

with exercise capacity, suggesting a role in the reduced peripheral perfusion characteristic of heart failure. Importantly, elevated ET-1 and big ET-1 levels are strong and independent predictors for patient survival. In addition, blocking ET-1 effects by ET-1 receptor antagonists caused haemodynamic improvement in patients with heart failure^[8] and improved survival in rats with heart failure induced by a large myocardial infarction^[9,10], i.e. in the model that predicted the clinical effects of ACE-inhibitors. Finally, it was shown that a polymorphism of the ET_A receptor gene on exon 8 (+1363 C/T) was associated with non-ischaemic dilated cardiomyopathy with a significant increase in the number of T/T homozygotes among patients, particularly in younger subjects in whom genetic factors are expected to be of importance^[11]. Thus, a multitude of data suggest that the endothelin system is intricately involved in the pathophysiology of human heart failure and removing its influence on the cardiovascular system may prove beneficial.

It is against this background that the data reported in this issue by [Herrmann and colleagues](#)^[12] are of special interest. They found that a genetic variant of the ET_A receptor, e.g. the H323H (H/T) polymorphism in exon 6 of the ET_A receptor gene, had a marked and significant influence on survival in a cohort of patients with non-ischaemic dilated cardiomyopathy. Carriers of the less frequent ET_A receptor T allele had a more than fivefold increased risk of dying within 2 years after presenting with the diagnosis and this effect was independent from other predictors of survival in such patients. In contrast, five other polymorphisms of the ET-1 gene, the ET_A and the ET_B receptor had no influence on survival.

An association of a genetic variant with survival in patients with heart failure has been noted before and the data resemble those found for another key cardiovascular signalling element in heart failure, e.g. the Ile164 β_2 -adrenoceptor polymorphism which was also associated with poor survival in patients with chronic heart failure^[13]. What conclusions can be drawn from findings like these? Obviously, the possibility of using the presence of such a genetic variant for risk assessment in patients appears attractive. Theoretically, patients carrying the T allele might be candidates for earlier aggressive interventions including transplantation. It is also conceivable that the presence of this genetic variant might influence the response to ET-1 receptor antagonists if these compounds are to be used therapeutically in heart failure patients in the future. However, before accepting these contentions one must recall that each individual carries a library of genetic polymorphisms, most of which are irrelevant for the disease in question. Thus, certain criteria should be met before a genetic change

can be linked with a disease trait. Firstly, the polymorphism should result in an alteration of the gene product. Secondly, the relationship between the genetic alteration and the corresponding phenotype should be strong, and, thirdly, the association must be biologically plausible.

Based upon the evidence presented earlier, there is no major objection to the biological plausibility of the reported association. How about the other criteria? As the authors note, the H323H (H/T) polymorphism in exon 6 of the ET_A receptor gene does not change the amino acid sequence of the receptor. Functional studies of this variant are not available but it is likely that receptor function is not altered unless this variant influences gene transcription or creates a novel splice site. Alternatively, as the authors suggest, this finding could mean that this polymorphism co-segregates with another functionally active but so far unidentified genetic variant and, therefore, acts as a marker for some other deleterious trait. As for the association between the genetic variant and the phenotype, the data appears fairly strong with a risk ratio for death of 5.5 for carriers of the ET_A T allele. However, the number of deaths on which the analysis is based is small and the lower 95% confidence interval barely does not include 1. Moreover, the study may be criticized from a statistical point of view as the authors examined six polymorphisms. Thus, based on multiple testing and a 5% chance for each test to yield a false positive result, there was a chance of up to 30% for a false positive finding. Finally, although the authors could demonstrate that haemodynamic and structural cardiac changes had no impact on the strength of this association they did not investigate other well proven markers of survival in heart failure patients such as plasma levels of natriuretic peptides, and ET-1 and big ET-1. It is obvious that the relationship between activation of the endothelin-1 system and this genetic polymorphism would have been of particular interest.

Taken together, it appears that the reported association of this genetic variant and survival in patients with non-ischaemic dilated cardiomyopathy is intriguing but can by no means be considered to be proven. Interestingly, the (G+70C) polymorphism of the ET_A receptor gene had no influence on survival in this study. This variant is in close linkage disequilibrium with the (+1363 C/T) variant on exon 8 of the ET_A receptor gene, the T/T variant of which was more frequently found in patients with dilated cardiomyopathy than in control subjects^[11]. Whether this indicates that some ET_A receptor gene variants are involved in the development of the phenotype, i.e. non-ischaemic dilated cardiomyopathy, and others, like the currently investigated variant, which are

important for the development of disease complications, is an attractive but clearly unproven hypothesis.

Where will findings like these lead us? Certainly, additional studies will follow and it is to be hoped that a reasonably clear picture of the influence of genetic variants of the endothelin system on the development of the disease and its complications will emerge. This does not necessarily have to be the case, as shown for another well publicized genetic polymorphism in cardiovascular diseases, namely the insertion (I)/deletion (D) polymorphism of the angiotensin converting enzyme gene. After many early positive reports about the association of the DD variant with a variety of cardiovascular disorders, among them myocardial infarction, hypertension, and left ventricular hypertrophy subsequent studies in additional populations have been frequently inconsistent (for review^[14]). Also, it emphasizes our incomplete understanding of the interaction of genetic changes with disease phenotypes. The other genetic variant associated with poor survival in heart failure, e.g. the Ile164 β_2 -adrenoceptor polymorphism, results in a loss of receptor function^[15]. This makes understanding the beneficial clinical effects of pharmacologically induced loss of function, e.g. beta-blocker therapy, somewhat difficult. Thus, future research will not only have to show that this genetic variant of the ET_A receptor gene truly influences survival, but should also provide meaningful insights into the mechanisms whereby genetic factors interact with the development of heart failure and its complications.

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